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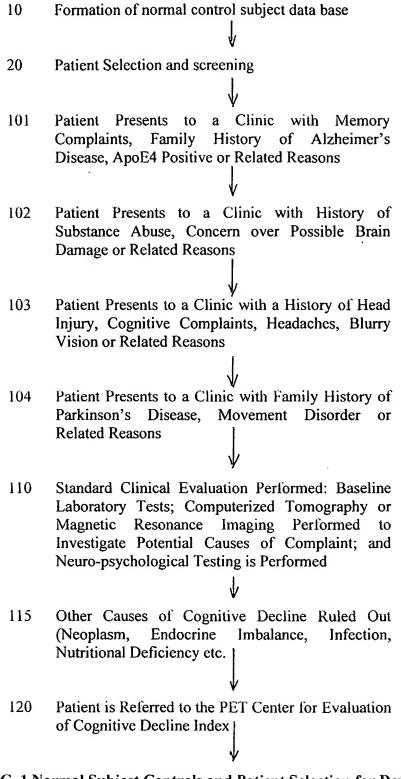


FIG. 1 Normal Subject Controls and Patient Selection for Development of the Cognitive Decline Index

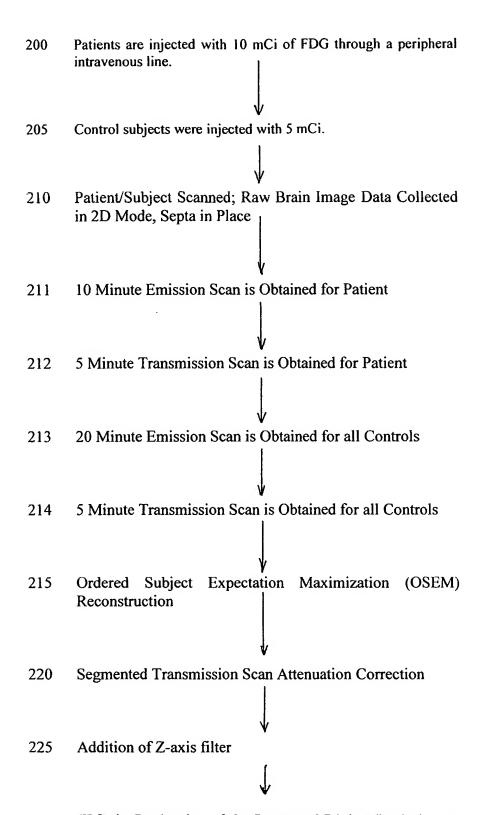


FIG. 2a Derivation of the Processed Digital Brain Image

230	GE Advance Workstation (Sun <sup>TM</sup> Ultra 60), and a Copy Prepared for Export to the Research Workstation for Use
	with SPM
235	Copy Prepared for Export to the Research Workstation for Use with SPM
	Ose with Si M
	$\bigvee$
240	Scans Converted to Analyze 7.5 <sup>TM</sup> (Analyze Direct, LENEXA KS) Format
245	June 1 American Continue Dunescood and American with
245	Images Are then further Processed and Analyzed with SPM99 (SPM, Friston et al, 1995a) and Implemented in
	Matlab
	V
250	Management of the Image Data is Achieved by Utilizing the Digital Imaging and Communication in Medicine
	(DICOM) Format
260	Convert to Signed, 16-bit, "Byte-swapped" Image
265	Ψ "Byte-swapping" Option Taken Depending on Workstation
	Туре
	$\bigvee$
270	Image Transformed into Talairach Space
280	√ Image Spatially Transformed using Gaussian Kernel
	inabe changing removement assure component recines

FIG. 2a (Cont'd) Derivation of the Processed Digital Brain Image

300	SPM Group Analysis: Patients Compared to Normal Controls								
310	Extrema in Changes in Metabolic Brain Activity Evaluated								
	$\downarrow$								
320	SPM(Z) Maps Created; Tables of Regional Maxima Compiled								
330	Convert to Normal Distribution Z-score								
340	Identification and Location of Clusters with Highest Significance Using Significance Thresholds Uncorrected for Multiple Comparisons								
350	Coordinates of Locations of Significant Interest Identified								
	from SPM results listing all maxima greater than 8mm apart								
	$\downarrow$								
360	Specific Loci from this Analysis are Used as Centers for 3-D, 1 cm Diameter Spherical (VOIs)								
	↓								
370	Identification of Specific Loci in Brain as Volumes of Interest (VOI) created with the Marsbar <sup>©</sup> plug-in (Bret et al, 2002) for SPM								
	↓								
380	Intensity of Each of the Voxels within the Spherical VOI is Read and the Average is Obtained								
	$\bigvee$								
390	Weights (Set CDI <sub>1</sub> ) for each VOI are Calculated Based on the Frequency of Abnormality of the VOI Data from All the Study Patients as Compared to All Controls with Greater Weight Given to Increased Frequency as Determined by Intensity Range Overlap for each Volume of Interest Ratio								

FIG. 2b Derivation of Region Location and Identification of VOIs

- 391 Import VOI Data Into Spreadsheet
- 392 Determine Intensity Range Overlap for each VOI Ratio
- 393 Create Weights for each Intensity Extreme
- 394 Create Weighted VOI Ratio
- 395 Scale and Normalize Ratio
- Calculation of CDI: 400

$$CDI = C_x + \left[ \sum_{j=1}^{n} V_j X_j / n \right] / \left[ \sum_{i=1}^{m} W_i Y_i / m \right]$$

Where  $X_j$  denotes the  $j^{th}$  Increased Intensity Value;  $V_j$  denotes the  $j^{th}$  Weight for the  $j^{th}$  Increased Intensity Value;

Y<sub>i</sub> denotes the i<sup>th</sup> Decreased Intensity Value; and

W<sub>i</sub> denotes the i<sup>th</sup> Weight for the i<sup>th</sup> Decreased Intensity Value.

C<sub>x</sub> is the correction factor used to normalize the dataset.

410 Weights of Set CDI<sub>1</sub> are then used as a baseline for calculation of a second set of Weights (Set CDI<sub>2</sub>) to calculate CDI<sub>2</sub>. Set CDI<sub>2</sub> is calculated by iterative optimization of each weight to maximally separate the patient from the controls

FIG. 2b (Cont'd) **Derivation of Region Location and Identification of VOIs**  500 CDI is Compared to Established Normal Range of Values; Presence of Normality or Abnormality is Determined

510 If CDI Reading is Negative, Patient Educated About the Clinical Course of Potential Illnesses and Signs to Watch out for; Potential Benefit of Preventative Measures such as Antioxidants, Brain Exercises, Beneficial Diet and Adequate Rest are Discussed



520 If CDI Reading is Positive, Patient Educated about the Meaning of a Positive CDI Reading, Projected Clinical Course of Illness, Benefit of Medication, Potential Benefit of Preventative Measures such as Antioxidants, Brain Exercises, Beneficial Diet and Adequate Rest are Discussed



Following either Step 620 or Step 630, Results are Given to Referring Physician and Patient Scheduled for Reevaluation in one year.



540 Patient Data is Stored in the Comprehensive Patient Database

#### FIG. 2c Patient Diagnosis and Clinical Recommendations

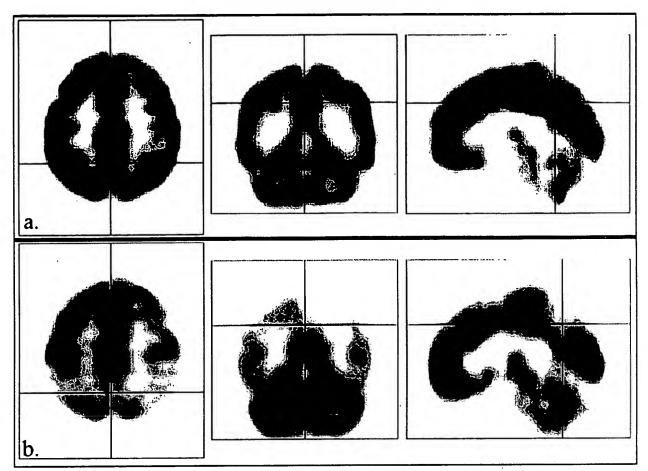
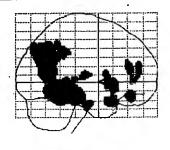
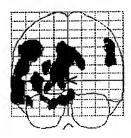
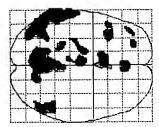


Fig. 3

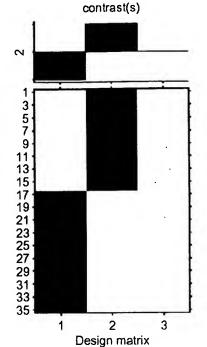




SPMmip [0, 0, 0]



SPM{T33}



**SPMresults** sults 122802 MCIvsOldctrls Height threshold T = 2.50 Extent threshold k = 50 voxels

Statistics: volume summary (p-values corrected for entire volume)

set-level		cluster-level		voxel-level				x,y,z {mm}	
p	С	P corrected	k <sub>F</sub>	p uncorrected	p corrected	T	(Z_)	P uncorrected	
0.173	14	0.000	1945	0.000	0.106	5.29	( 4.47)	0.000	-4 -70 30
		••••			0.483	4.54	( 3.97)	0.000	-14 -68 16
					0.616	4.37	( 3.86)	0.000	-4 -58 28
		0.000	2610	0.000	0.788	4.16	(3.70)	0.000	-42 -74 36
					0.804	4.13	(3.68)	0.000	-56 -56 16
					0.881	4.01	(3.59)	0.000	·-60 -56 -8
		0.862	202	0.064	0.883	4.01	(3.59)	0.000	-6 14 -24
		0.247	450	0.009	0.951	3.84	(3.47)	0.000	52 -64 38
					1.000	2.96	( 2.77)	0.003	54 -50 44
		1.000	58	0.302	0.998	3.49	( 3.20)	0.001	-48 18 -22
		0.991	114	0.153	0.998	3.48	(3.19)	0.001	-4 - 12 10
					1.000	2.81	( 2.64)	0.004	-8 -30 4
. *		0.996	101	0.177	.0.999	3.43	(3.15)	0.001	4 38 -16
		0.944	162	0.093	1.000	3.37	( 3.10)	0.001	-10 14 -2
					1.000	2.90	( 2.71)	0.003	-12 8 12
		0.981	131	0.127	1.000	3.32	(3.07)	0.001	-20 -14 -28
					1.000	2.91	( 2.72)	0.003	-30 -22 -20
		0.888	191	0.071	1.000	3.22	(2.98)	0.001	-38 20 -2
		0.997	95	0.189	1.000	3.21	( 2.97)	0.001	-26 48 16
		0.993	110	0.160	1.000	3.05	( 2.84)	0.002	-2 36 18
					1.000	2.69	( 2.54)	0.006	-2 42 2
		1.000	69	0.261	1,000	3.00	( 2.80)	0.003	-24 -38 -6
		1.000	50	0.338	1.000	2.93	(2.74)	0.003	-40 46 6

table shows at most local maxima > 8.0mm apart per cluster

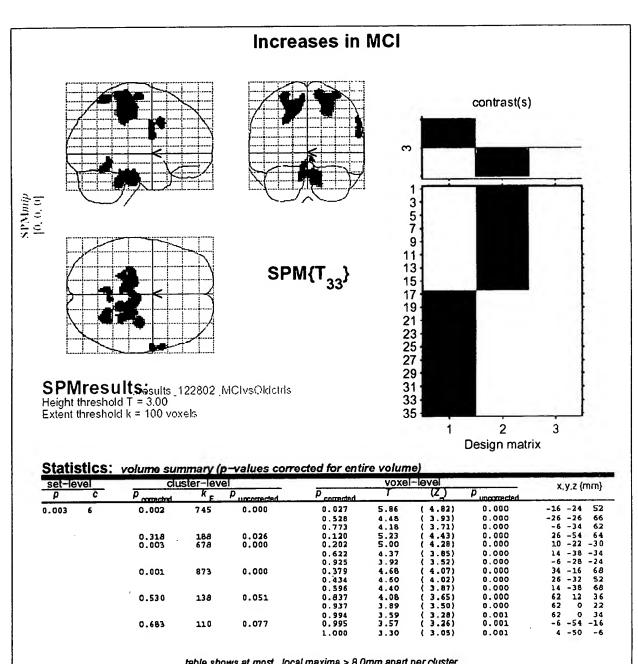
Height threshold: T = 2.50, p = 0.009 (1.000 corrected)
Extent threshold: k = 50 voxels, p = 0.338 (1.000 corrected)
Expected voxels per cluster, <k> = 58.849

Expected number of clusters, <c> = 10.48

Degrees of freedom = [1.0, 33.0]
Smoothness FWHM = 13.5 13.7 16.0 {mm} = 6.7 6.9 8.0 {voxels}
Search volume: S = 1815544 mm^3 = 226943 voxels = 559.8 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 370.95 voxels)

Statistics: single cluster summary (p-values corrected for entire volume)

clu	cluster-level			voxel-level			
P corrected	K <sub>F</sub>	Puncorrected	P corrected	T	(Z)	Puncorrected	x,y,z (mm)
0.000	2610	0.000	0.788	4.16	( 3.70)	0.000	-42 -74 36
			0.804	4.13	( 3.68)	0.000	-56 -56 16
			0.881	4.01	(3.59)	0.000	-60 -56 -8
•			0.892	3.99	( 3.58)	0.000	-62 -36 -6
			0.905	3.96	(3.56)	0.000	-64 -30 -22
			0.938	3.89	( 3.50)	0.000	-58 -46 -22
F16	)/		0.977	3.74	(3.39)	0.000	-50 -60 42
F 110	$\neg$		0.987	3.66	(3.33)	0.000	-42 -62 44
	/		0.998	3.50	( 3.21)	0.001	-52 -62 28
,			1.000	3.03	(2.83)	0.002	-56 -46 36
			1.000	3.01	( 2.81)	0.002	-54 -68 16
			1.000	2.99	( 2.79)	0.003	-62 -24 -8
			1.000	2.83	( 2.66)	0.004	-62 -18 -24
			1.000	2.76	( 2.60)	0.005	-32 -56 40



Degrees of freedom = [1.0, 33.0] Smoothness FWHM = 13.5 13.7 16.0 {mm} = 6.7 6.9 8.0 {voxels} Search volume: S = 1815544 mm\*3 = 226943 voxels = 559.8 resels Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 370.95 voxels)

Fig. 5

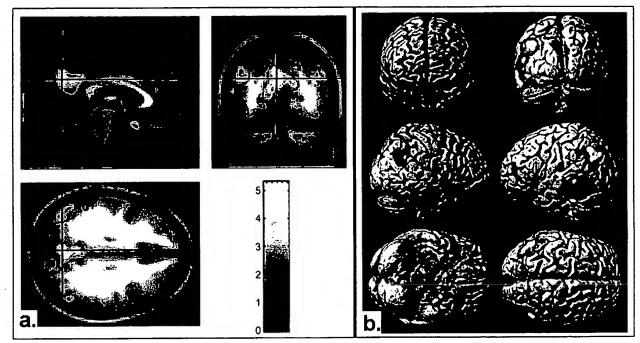


Fig. 6

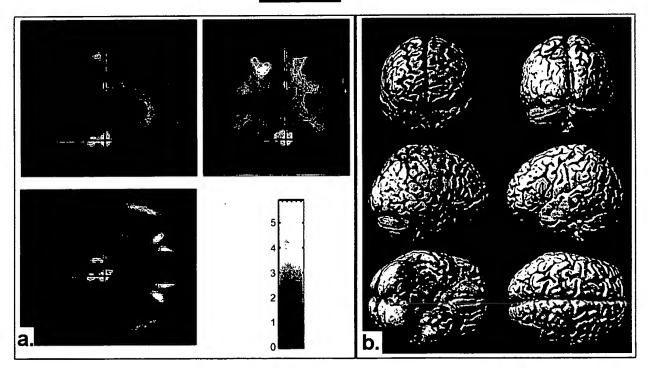
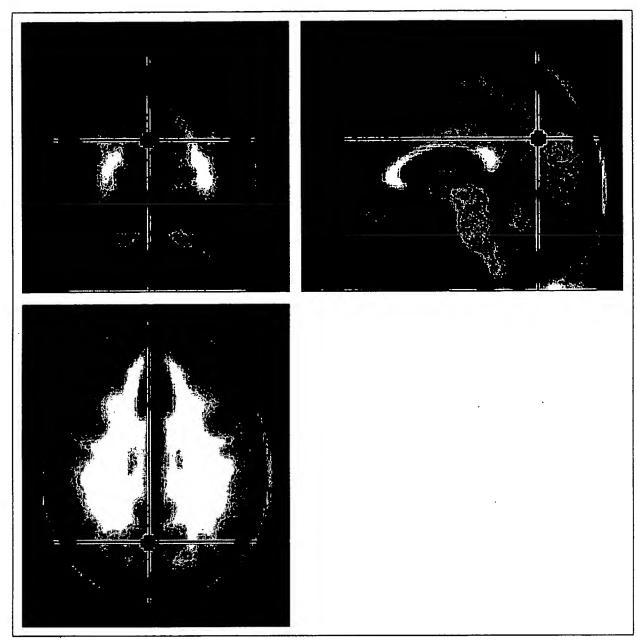
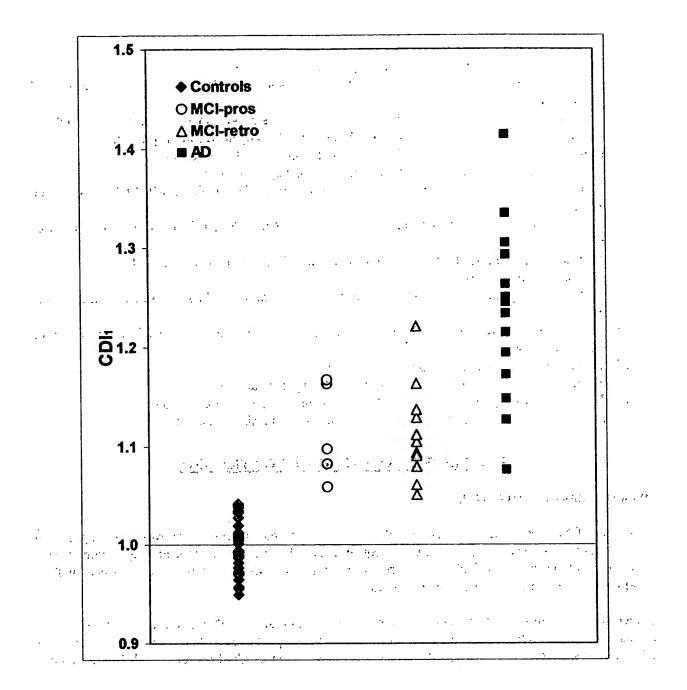


Fig. 7



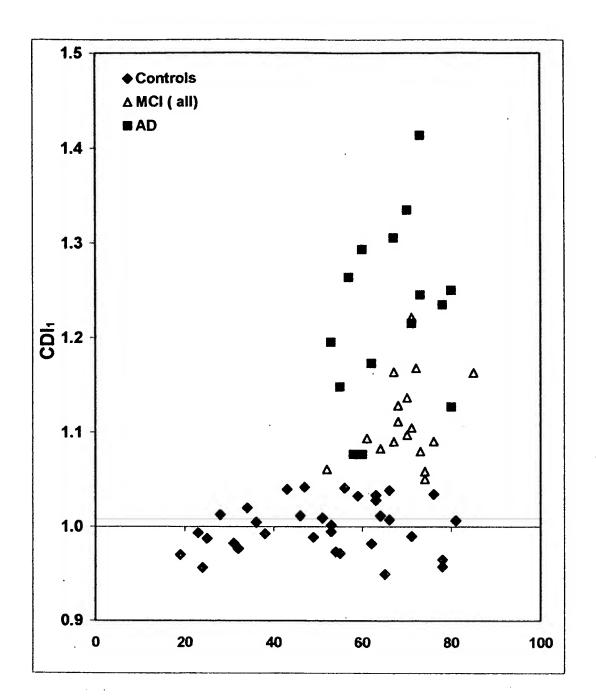
**Fig. 8** 



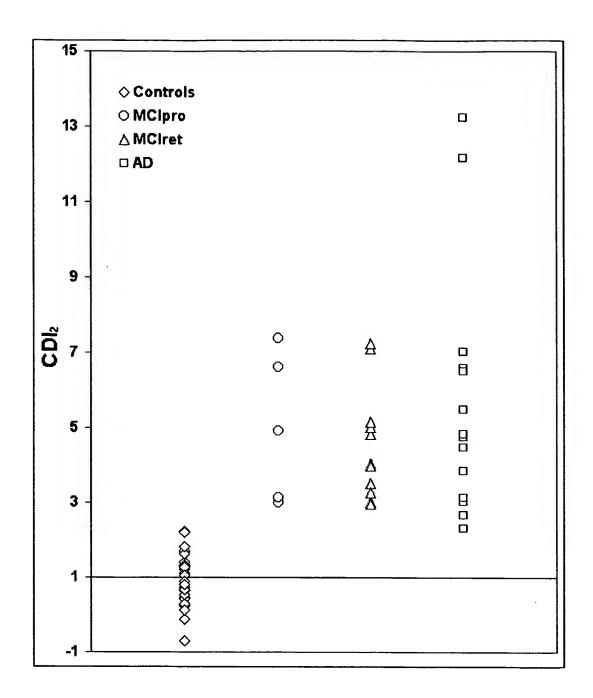
F16.9

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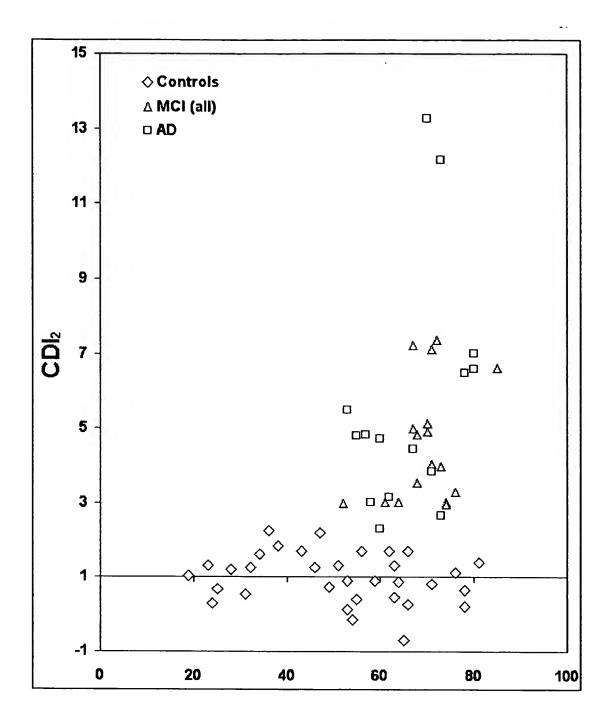
#### 医克雷特勒氏 化二氯甲基邻基酚 化二氯甲基氯酚 化二氯酚 不足



F16.10



F16.11



F16.12